WO 03/061639 PCT/CA03/00079

- 16 -

We Claim:

- 1. Use of a glutathione-increasing compound and a nitric oxide increasing compound in the manufacture of a medicament useful in the treatment of insulin resistance.
- 2. Use of a glutathione-increasing compound and a nitric oxide-increasing compound in improving glucose uptake in a patient suffering from insulin resistance.
- 3. Use of claim 1 or 2 wherein the insulin resistance is hepatic insulin sensitizing substance ("HISS")-dependent insulin resistance.
- 4. Use of claim 1, 2 or 3 wherein the glutathione-increasing compound is at least one of N-acetylcysteine, cysteine esters, L-2-oxothiazolidine-4-carboxolate ("OTC"), gamma glutamylcysteine and its ethyl ester, glutathione ethyl ester, glutathione isopropyl ester, lipoic acid, cystine, cysteine, methionine, and S-adenosylmethionine ("SAMe").
- Use of claim 1, 2, 3 or 4 wherein the nitric oxide-increasing compound is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, nitrosylated cysteine esters, nitrosylated L-2-oxothiazolidine-4-carboxolate (NOTC), nitrosylated gamma glutamylcystein and its ethyl ester, nitrosylated glutathione ethyl ester, nitrosylated glutathione isopropyl ester, nitrosylated lipoic acid, nitrosylated cysteine, nitrosylated cystine, nitrosylated methionine, or nitrosylated S-adenosylmethionine.
- 6. A pharmaceutical composition comprising a hepatic glutathione increasing compound and a hepatic nitric oxide-increasing compound.
- 7. A pharmaceutical composition comprising at least one of nitrosylated N-acetylcysteine, nitrosylated cysteine esters, nitrosylated L-2-oxothiazolidine-4-carboxolate (NOTC), nitrosylated gamma glutamylcystein and

its ethyl ester, nitrosylated glutathione ethyl ester, nitrosylated glutathione isopropyl ester, nitrosylated lipoic acid, nitrosylated cysteine, nitrosylated cysteine, nitrosylated s-adenosylmethionine.

- 8. The pharmaceutical composition of claim 6 or 7 further including a pharmaceutically acceptable antioxidant.
- 9. A method of reducing insulin resistance in a mammalian patient having lower than normal hepatic glutathione levels, said method comprising:

selecting a patient suffering from insulin resistance;

determining if hepatic glutathione levels are lower than normal in the patient; and

administering a compound which increases hepatic glutathione and a compound which increases hepatic nitric oxide.

- 10. A method of reducing insulin resistance in a mammalian patient comprising administering a compound which increases hepatic glutathione and a compound which increases hepatic nitric oxide ("NO").
- 11. The composition of claim 6, 7 or 8 further including a pharmaceutically acceptable liver-targeting substance.
- 12. The method of claim 9 wherein the insulin resistance is HISS-dependent insulin resistance ("HDIR").
- 13. The method of claim 12 wherein the hepatic glutathione-increasing compound administered causes an increase in hepatic glutathione synthesis.
- The method of claim 10, 11 or 12 wherein the glutathione-increasing compound is at least one of N-acetylcysteine, cysteine esters, L-2-oxothiazolidine-4-carboxolate ("OTC"), gamma glutamylcysteine and its ethyl ester, glutathione ethyl ester, glutathione isopropyl ester, lipoic acid, cystine, cysteine, methionine, and S-adenosylmethionine ("SAMe").

- The method of claim 10, 11, 12, 13 or 14 wherein the nitric oxide-increasing compound is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, nitrosylated cysteine esters, nitrosylated L-2-oxothiazolidine-4-carboxolate (NOTC), nitrosylated gamma glutamylcystein and its ethyl ester, nitrosylated glutathione ethyl ester, nitrosylated glutathione isopropyl ester, nitrosylated lipoic acid, nitrosylated cysteine, nitrosylated cystine, nitrosylated methionine, or nitrosylated S-adenosylmethionine.
- 16. The method of any preceding claim wherein the glutathione-increasing compound is administered orally.
- 17. The method of any preceding claim wherein the glutathione-increasing compound is administered by intravenous injection.
- 18. The method of any preceding claim wherein the glutathione-increasing compound is 8-bromo-cGMP.
- 19. The method of any preceding claim wherein the compound which increases hepatic NO is administered orally.
- 20. The method of any preceding claim wherein the compound which increases hepatic NO is administered by intravenous injection.
- 21. The method of any preceding claim wherein the compound which increases nitric oxide is SIN-1.
- 22. The method of any preceding claim wherein the compound which increases hepatic NO is molsidamine.
- 23. The method of any preceding claim further including administering a pharmaceutically acceptable anti-oxidant.

PCT/CA03/00079

- 24. The method of any preceding claim wherein the patient suffers from at least one of non-insulin dependent diabetes, essential hypertension, metabolic obesity, chronic liver disease, fetal alcohol effects, old age and a chronic inflammatory disease.
- 25. The method of any preceding claim wherein the patient is a human.